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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,170	11/10/2000	Raymond P. Warrell	10412-025	4982

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EXAMINER	
GIBBS, TERRA C	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,170	WARRELL ET AL.	
	Examiner	Art Unit	
	Terra C. Gibbs	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-23 and 29-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-23 and 29-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on May 10, 2004 has been entered.

Claims 1-23 and 29-33 are pending in the instant application. Claims 24-28 were previously canceled. Claims 1-3, 18, 19, 29,30, and 33 have been amended.

Claims 1-23 and 29-33 have been examined on the merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Response to Amendment

Applicants Amendment filed May 10, 2004 has been considered. Rejections and/or objections not reiterated from the previous office action mailed December 15, 2003 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

Claim Rejections - 35 USC § 102

In the previous office action mailed December 15, 2003, claims 1-5 and 13-18 were rejected under 35 U.S.C. 102(b) as being anticipated by Webb et al., (The Lancet, 1997 Vol. 349:1137-1141). **This rejection is maintained against claims 1, 4, 5, and 13-18, but withdrawn against claims 2 and 3** in view of Applicants arguments.

Response to Arguments

In response to the 35 U.S.C. 102(b) rejection against claims 1-5 and 13-18 as being anticipated by Webb et al. (The Lancet, 1997 Vol. 349:1137-1141), Applicants argue that the Examiner has mischaracterized the teachings of Webb et al. Applicants contend that Webb does not teach two cycles of therapy each lasting 7 days for a total of 14 days, but rather Webb teaches a one 2-week course of treatment. Applicants argue that Webb teaches treating a human with one cycle of therapy for 14 days. Applicants argue that given that Webb does not teach or suggest a cycle of therapy consisting of 2 to 13 days, this grounds of rejection be withdrawn.

Applicant's arguments have been fully considered and are found persuasive. The Examiner agrees that Webb teaches treating a human with one cycle of therapy for 14 days. In view of this, this rejection has been withdrawn against claims 2 and 3. However, this rejection is maintained against claims 1, 4, 5, and 13-18 for the following reasons: As Applicants has eluded, Webb teaches treating a human with one cycle of therapy for 14 days. The instant claims are drawn to treating a human with one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. The Examiner would like to direct Applicants to MPEP §2111.03 where it states:

> The transitional phrase "consisting essentially of" limits the scope of a claim to the specified materials or steps "and those that do not materially affect the basic and novel characteristic(s)" of the claimed invention. *In re Herz*, 537 F.2d 549, 551-52, 190 USPQ 461, 463 (CCPA 1976).
>
> If an applicant contends that additional steps or materials in the prior art are excluded by the recitation of "consisting essentially of," applicant has the burden of showing that the introduction of additional steps or components would materially change the characteristics of applicant's invention. *In re De Lajarte*, 337 F.2d 870, 143 USPQ 256 (CCPA 1964). See also Ex parte Hoffman, 12 USPQ2d 1061, 1063-64 (Bd. Pat. App. & Inter. 1989).
>
> For the purposes of searching for and applying prior art under 35 U.S.C. 102 and 103, absent a clear indication in the specification or claims of what the basic and novel characteristics actually are, "consisting essentially of" will be construed as equivalent to "comprising." See, e.g., PPG, 156 F.3d at 1355, 48 USPQ2d at 1355.

In the instant case, the difference between the disclosure of Webb et al. and what is claimed in the instant claims is only plus or minus one day of therapy. The Examiner believes that it is Applicants contention that the instant claims are novel over Webb et al. because the claims recite treating a human with one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, as opposed to treating a human with one cycle of therapy for 14 days, as disclosed by Webb et al. Applicant has the burden of showing that the introduction of additional steps or components disclosed by Webb would materially change the characteristics of applicant's invention.

In this regard, Webb et al. anticipate claims 1, 4, 5, and 13-18.

Claim Rejections - 35 USC § 103

In the previous office action mailed December 15, 2003, claims 1, 6-11 and 13-18 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Jansen et al. (Proceedings of the American Society of Clinical

Oncology, 1999 Vol. 19:531a). Claims 1, 6, 10, 12, 19 and 29-33 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., and Jansen et al. as cited in the 35 U.S.C. 103(a) rejection against claims 6, 9, 10 and 11 in further view of Klasa et al. (Clinical Cancer Research, 2000 Vol. 6:2492-2500). Claims 19-23 were rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., Jansen et al., and Klasa et al., in further view of Tortora et al. (Antisense and Nucleic Acid Drug Development, 1998 Vol. 8:141-145); Adjei et al. (Seminars in Oncology, 1999 Vol. 26:32-40); Foran et al. (Journal of Clinical Oncology, 1999 Vol. 17:546-53); or Murren et al. (Caner Chemotherapy Pharmacology, 2000 Vol. 46:43-50). **All of these rejections are withdrawn** in view of the new 35 U.S.C. 103(a) rejection below:

Claim Rejections - 35 USC § 103

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-23 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

Claim 1 is drawn to a method of treating or preventing cancer in a human comprising administering a bcl-2 antisense oligonucletoide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 2-18 are dependent on claim 1 and include all the limitations of claim 1, with the further limitations

wherein one or more cycles of therapy consist of 3 to 9 days; wherein one or more cycles of therapy consist of 4 to 7 days; wherein the bcl-2 antisense oligonucletoide is administered at a dose of 4 to 9 mg/kg/day; wherein the bcl-2 antisense oligonucletoide is administered at a dose of 5 to 7 mg/kg/day; and further comprises administering one or more cancer therapeutics. Claim 19 is drawn to a method of treating or preventing cancer in a human comprising administering one or more chemoagents and a bcl-2 antisense oligonucletoide, wherein the bcl-2 antisense oligonucletoide is administered at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days. Claims 20-23 are dependent on claim 19 and include all the limitations of claim 19, with the further limitations of specific chemoagents, and specific doses of chemoagents.

Webb et al. teach treating human patients with non-Hodgkin's lymphoma with one cycle of bcl-2 antisense therapy for 14 days. Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings). Webb et al. do not teach wherein one or more cycles of therapy consist of 3 to 9 days; wherein one or more cycles of therapy consist of 4 to 7 days, wherein the bcl-2 antisense oligonucleotide is administered at a dose of 4 to 9 mg/kg/day; or wherein the bcl-2 antisense therapy further comprises administering one or more cancer therapeutics.

In the instant case, the difference between the disclosure of Webb et al. and what is claimed in the instant claims is only plus or minus one day of therapy. The Examiner believes that it is Applicants contention that the instant claims are novel over Webb et al. because the claims recite treating a human with one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, as opposed to treating a human with one cycle of therapy for 14 days,

as disclosed by Webb et al. Applicant has the burden of showing that the introduction of additional steps or components disclosed by Webb would materially change the characteristics of applicant's invention. See MPEP §2111.03.

Bennett et al. teach the antisense modulation of bcl-x expression using therapeutic compositions comprising antisense nucleic acids. Bennett et al. also teach "the formulation of therapeutic compositions and their subsequent administration is believed to be within the skill of those in the art. Dosing is dependent on severity and responsiveness of the disease state to be treated, with the course of treatment lasting from several days to several months, or until a cure is effected or a diminution of the disease state is achieved. Optimal dosing schedules can be calculated from measurements of drug accumulation in the body of the patient. Persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. Optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models. In general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. Persons of ordinary skill in the art can easily estimate repetition rates for dosing based on measure residence times and concentrations of the drug in bodily fluids or tissues" (see columns 16-17, last and first paragraphs, respectively). Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics, including doxorubicin, 5-fluorouracil (5-FU), etoposide, and cisplatin, for example (see column 16, lines 28-52). Bennett et al. teach bcl antisense oligonucleotides are administered with prodrugs (see columns 11 and 12, last and first paragraphs, respectively).

It would have been obvious to one of ordinary skill in the art to devise a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucletoide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days as taught by Webb et al. It would have been obvious to vary the cycles of therapy to consist of 3 to 9 days or 4 to 7 days, or to vary the antisense oligonucleotide dosage amount since it is routine and well known in the art to determine optimum dosages, dosing methodologies, and repetition rates based on measured residence times and concentrations of the drug in bodily fluids or tissues. It would have been obvious to vary the cycles of therapy to consist of 3 to 9 days or 4 to 7 days, or to vary the antisense oligonucleotide dosage amount since Bennett et al. teach, in general, dosage is from 0.01 μg to 100 g per kg of body weight, and may be given once or more daily, weekly, monthly or yearly, or even once every 2 to 20 years. It would have been further obvious to administer antisense therapy further comprising administering one or more cancer therapeutics or chemoagents since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment.

One skilled in the art would have been motivated to devise a method of treating cancer in a human comprising administering a bcl-2 antisense oligonucletoide at a dose of 0.01 to 50 mg/kg daily in one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days because Webb et al. explicitly teaches treating human patients with non-Hodgkin's lymphoma with one cycle of bcl-2 antisense therapy for 14 days. Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days. It is noted that the difference between the disclosure of Webb et al. and what is claimed in the instant claims is only plus or minus one day of therapy. The Examiner believes that it is Applicants

contention that the instant claims are novel over Webb et al. because the claims recite treating a human with one or more cycles of therapy, each cycle of therapy consisting of 2 to 13 days, as opposed to treating a human with one cycle of therapy for 14 days, as disclosed by Webb et al. Applicant has the burden of showing that the introduction of additional steps or components disclosed by Webb would materially change the characteristics of applicant's invention. See MPEP §2111.03. One of ordinary skill in the art would be motivated to vary the cycles of therapy to consist of 3 to 9 days or 4 to 7 days, or to vary the antisense oligonucleotide dosage amount since Bennett et al. teach persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates because optimum dosages may vary depending on the relative potency of individual oligonucleotides, and can generally be estimated based on EC_{50s} found to be effective in *in vitro* and *in vivo* animal models.

Therefore, the invention of claims 1-23 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Claims 29-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Webb et al., (The Lancet, 1997 Vol. 349:1137-1141) in view of Bennett et al. [U.S. Patent No: 6,214,986].

Claims 29 and 30 are drawn to a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle consisting of 2 to 13 days, in combination with a cancer therapeutic agent, wherein the dose of the bcl-2 antisense is 0.01 to 50 mg/kg/day or 10 to 50 mg/kg/day, respectively. Claims 31-33 are dependent on either claim 29 or 30, and include all the limitations of claim 29 or 30, with the further limitations, wherein the pharmaceutical composition is form 10 to 40 bases in length and

is complementary to the bcl-2 gene; wherein the antisense oligonucletoide comprises at least two phosphorothioate linkages; and wherein the antisense comprises SEQ ID NO:17.

Webb et al. teach treating human patients with non-Hodgkin's lymphoma with one cycle of an 18-base, fully phosphorothioated bcl-2 antisense oligonucletoide for 14 days. Webb et al. further disclose the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2 for 14 days (see page 1137, Findings). It is noted that the bcl-2 antisense composition taught by Webb et al. is 100% identical to SEQ ID NO:17 of the instant invention. Webb et al. do not teach a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle consisting of 2 to 13 days, in combination with a cancer therapeutic agent.

Bennett et al. teach the antisense modulation of bcl-x expression using therapeutic compositions comprising antisense nucleic acids. Bennett et al. also teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics (see column 16, lines 28-52).

It would have been obvious to one of ordinary skill in the art to make a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle consisting of 2 to 13 days, wherein the dose of the bcl-2 antisense is 0.01 to 50 mg/kg/day as taught by Webb et al. It would have been obvious to vary the dosage of the pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy since Bennett et al. teach, in general, dosage is from 0.01 μg to 100 g per kg of body weight. It would have been obvious to administer the pharmaceutical comprising a bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent

since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment. It would have been further obvious to administer the pharmaceutical comprising a bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent since Bennett et al. explicitly teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics.

One skilled in the art would have been motivated to make a pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy, each cycle consisting of 2 to 13 days, wherein the dose of the bcl-2 antisense is 0.01 to 50 mg/kg/day because Webb et al. explicitly teaches treating human patients with non-Hodgkin's lymphoma with one cycle of an 18-base, fully phosphorothioated bcl-2 antisense oligonucletoide for 14 days, wherein the daily dose of bcl-2 antisense was increased incrementally from 4.6 mg/m^2 to 73.6 mg/m^2. One of skill in the art would have been motivated to vary the dosage of the pharmaceutical composition comprising a bcl-2 antisense oligonucleotide for administration for one or more cycles of therapy since Bennett et al. teach persons of ordinary skill can easily determine optimum dosages, dosing methodologies and repetition rates. One of skill in the art would have been further motivated to administer the pharmaceutical comprising a bcl-2 antisense oligonucleotide in combination with a cancer therapeutic agent since it is routine and well known in the art that combination therapy is an effective approach for cancer treatment and since Bennett et al. explicitly teach bcl antisense oligonucleotides are administered with one or more cancer therapeutics.

Therefore, the invention of claims 29-33 would have been obvious to one of ordinary skill in the art, as a whole, at the time the instant invention was made.

Conclusions

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Terra C. Gibbs whose telephone number is (571) 272-0758. The examiner can normally be reached on M-F 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (571) 272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

tcg
July 21, 2004

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